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(54) **Calciumphosphatidylchlorine-chloride, process for producing the same and pharmaceutical preparations containing the same**

(57) The present invention provides the new compound calcium phosphatidylcholine chloride as well as a process for producing the same wherein phosphatidylcholine and calcium chloride are reacted in a suitable solvent e.g. an aliphatic alcohol or water and pharmaceutical preparations containing the same.

GB 2 065 659 A

SPECIFICATION

Calcium phosphatidylcholine chloride, process for producing the same and pharmaceutical preparations containing the same

The present invention is directed to a solid, free-flowing calcium phosphatidylcholine chloride product of high purity which may be readily converted to pharmaceutical preparations. The present invention is further directed to processes for the production of this product and pharmaceutical preparations containing the same.

Lecithin products are phosphorus containing lipids which occur widely in living subject matter as well as in plants. In view of their high physiological importance in various processes of human life, the lecithins have been used for many years in the food industry.

Lecithin products as currently marketed represent a mixture of various components comprising about 35% of oil, phosphatidyl ethanolamine, phosphatidylcholine, phosphatidylinosite, phosphatidic acid, phosphatidylserine, sterines and other lipids (see for instance Seifen-Ole-Fette-Wachse 1973, vol. 99/6, p.168 to 169). However, only phosphatidylcholine is therapeutically interesting and important from a nutritive physiological point of view (see H. Peters "Phosphatidylcholine", Spring-Verlag 1976).

Phosphatidylcholine is recovered on a large scale as follows:
Oil is at first extracted from lecithin containing products by means of acetone. The fraction which is insoluble in acetone thereafter is extracted with ethanol and the extracts are purified by adsorption chromatography. The eluate then is evaporated giving substantially pure phosphatidylcholine. However, the phosphatidylcholine produced in this manner shows some considerable disadvantages. It is obtained as plastic material which has low stability and is difficult to further process and handle. Therefore, various efforts have been made to convert this plastic material into a free flowing powder or a liquid of low viscosity by the addition of various auxiliary agents. For instance, proteins have been added (see Japanese Patents Nos. 59/8884 and 62/12401 and USP 2 632 705) or mono- or polysaccharides have been used (see USP 2 430 553, 2 057 695 and 3 012 888). All these auxiliary agents however have the disadvantage that they either have to be added in large amounts up to 60% or that they are not acceptable physiologically and therefore cannot be used in pharmaceutical preparations. A further disadvantage of the above process is the use of acetone because acidic phosphatides may cause acetone to form condensation products such as mesityloxide or diacetone alcohol. Phosphatidylcholine obtained according to the above process is contaminated with such condensation products which are not only undesired organoleptically but also have a high toxicity even in small amounts and therefore have to be removed. This purification causes additional costs and work.

It is furthermore known (see German Patent 510 186 and Swiss Patents 127 256 and 136 239) that the usual lecithin addition product produced with calcium chloride is recovered as a solid pulervizable product by mixing an alcoholic solution of lecithin with an alcoholic solution of calcium chloride, treating the resulting solution with acetone and separating the precipitated addition compound from the solution and drying it. This process starts with the usual lecithin product which besides phosphatidylcholine further contains all other phosphatides such as phosphatidylethanolamine, phosphatidylserine, phosphatidylinosite and other accompanying lipids. There is obtained by this process therefore an addition compound of this phospholipid mixture with calcium chloride.

According to investigations of H. Hauser and R.M.C. Dafson (see European Journal of Biochemistry 1967, vol. 1, p.63) the affinity of the calcium ions does not exist for all phospholipids but the calcium ions are only bound by the acid phospholipids such as phosphatidic acid, phosphatidylserine, phosphatidylinosite and further accompanying lipids but not to non-acidic lipids such as phosphatidylcholine. The affinity of calcium ions to phosphatidic acid, phosphatidylserine and phosphatidylinosite is used for instance for the removal of such undesired accompanying lipids from lecithin (see USP 3 081 320). Based on these test results, it must be regarded as impossible to produce useful calcium chloride addition products with pure phosphatidylcholine.

It now has been found that, surprisingly in view of the above, there may be obtained a stable solid calcium phosphatidylcholine chloride of high purity by dissolving phosphatidylcholine in a suitable solvent and adding thereto a solution of calcium chloride in particular proportions and drying the resulting solution in the usual manner. There are obtained particularly favourable results by using an alcohol as solvent both for the phosphatidylcholine and for the calcium chloride, in particular a lower aliphatic alcohol, and by removing the alcohol without the addition of acetone from the resulting solution. A most preferred solvent is ethanol. The amount of calcium chloride added to the phosphatidylcholine is chosen such that the molar ratio of phosphatidylcholine to calcium chloride is between 1:0.5 and 1:2 and preferably 1:0.5, i.e. that 0.5 to 2 moles of calcium chloride are subjected to reaction with each mole of phosphatidylcholine. It is technically preferred to effect drying by means of a drum evaporator or in a spraydrying tower. A further advantage of the present process is that water or aqueous alcohol may be used as solvent in place of the aliphatic alcohol by emulsifying the phosphatidylcholine in an aqueous solution of calcium chloride and subjecting the resulting emulsion directly to drying in a spraydrying tower or to lyophilisation.

The new calcium phosphatidylcholine chloride which is produced by the present process furthermore may be processed more readily than pure phosphatidylcholine. It is a powder or granular product characterized by a high stability and may be readily used for pharmaceutical preparations in view of its high phosphatidylcholine content. The product may be ground, if necessary, to the desired particle

size. If desired, the powder or granular product may be compressed into tablets with the addition of usual galenic additives or may be filled into capsules. There may also be produced stable injection solutions by emulsifying the product in water. A further advantage of the product produced according to the present process is the absence of any acetone reaction products since of course acetone is not used during its preparation and, if such a reaction product was present in the starting material, any reaction product of acetone is separated from the calcium phosphatidylcholine chloride in the present process during the drying step.

The present invention is further illustrated by the following examples without however limiting the same thereto.

Example 1

8 kg (10 moles) of phosphatidylcholine and 1.1 kg (10 moles) of $CaCl_2$ are dissolved with stirring in 4500 cc. of ethanol. Ethanol is separated from the resulting solution by means of a drum dryer. The drying conditions are 120°C and 0.05 bar. There is obtained a slighly yellow flaky product which is ground in a hollow mill or a hammer mill to the desired grain size.

Analysis: P 3.49%; N 1.50% Ca 4.42%; Cl 7.55%.

After dissolving the product in chloroform and evaporating the solvent, the product shows unchanged analytical data.

The product is readily soluble in chloroform, may be dissolved with difficulty only in benzene, is insoluble in petroleum ether, ether and acetone and may be readily emulsified in water.

Example 2

8 kg (10 moles) of phosphatidylcholine and 0.55 kg (5 moles) of calcium chloride are dissolved in 3000 cc. of ethanol and the resulting mixture is further processed as described in Example 1.

Analysis: P 3.59%; N 1.70%; Ca 2.30%; Cl 4.02%.

Example 3

8 kg (10 moles) of phosphatidylcholine are emulsified in a solution of 1.1 kg (10 moles) of calcium chloride in 20,000 cc. of water and the resulting emulsion is spray dried in a spraydrying tower at 220°C. There is obtained a slightly yellow powder.

Example 4

8 kg (10 mols) of phosphatidylcholine and 0.55 kg. (5 moles) of calcium chloride are emulsified in 20,000 cc. of water and further processed as described in Example 3.

Example 5

The product obtained according to Example 2 is ground in a hollow mill, sieved (mesh size 0.5 mm), thoroughly mixed with 1% of Aerosil (finely powderous silicic acid with 99.9% of SiO_2 for adsorption purposes prepared by the German company Degussa AG of Frankfurt/Main, Federal Republic of Germany) and 2% of magnesium stearate and filled into capsules.

Example 6

100 g of calcium phosphatidylcholine chloride are emulsified in 900 cc. of water. The resulting solution is sterilised and filled into ampoules to obtain a 10% injection solution. If desired, vitamins and other trace products may be added to the injection solution.

CLAIMS

1. Calcium phosphatidylcholine chloride.
2. Calcium phosphatidylcholine chloride having the formula [PC]. $[CaCl_2]_x$ wherein PC is a phosphatidylcholine and x is a number from 0.5 to 2.
3. Calcium phosphatidylcholine chloride according to claim 1 which is obtained by subjecting phosphatidylcholine and calcium chloride to reaction in a suitble solvent and evaporating the resulting solution.
4. Calcium phosphatidylcholine chloride according to claim 3 wherein the phosphatidylcholine and calcium chloride are subjected to reaction in a molar proportion of 0.5 to 2 moles of calcium chloride per each mole of phosphatidylcholine.
5. Process according to claim 4 wherein the reaction is carried out in a suitable sovent and the resulting solution or emulsion is subjected to evaporation.
6. Process according to claim 5 wherein the solvent used is an aliphatic alcohol.
7. Process according to claim 6 wherein the solvent used is ethanol.
8. Process according to claim 5 wherein the solvent used is water.
9. Process according to any of claims 5 to 8 wherein phosphatidylcholine and calcium chloride are subjected to reaction in a molar ratio of 1 to 0.5.
10. Process according to any of claims 5 to 9 wherein evaporation is effected with a drum evaporator.
11. Process according to any of claims 5 to 9 wherein evaporation is effected by spraydrying.
12. Process according to any of claims 5 to 9 wherein drying is effected to lyophilisation.
13. Pharmaceutical preparations comprising a calcium phosphatidylcholine chloride according to any of claims 1 to 4 or produced by the process of any of claims 5 to 12.

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